

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 August 2006 (03.08.2006)

PCT

(10) International Publication Number
WO 2006/079637 A1

(51) International Patent Classification:

C07D 495/14 (2006.01) *A61P 25/18* (2006.01)
C07D 495/04 (2006.01) *A61P 25/22* (2006.01)
C07D 491/14 (2006.01) *A61P 25/24* (2006.01)
A61K 31/55 (2006.01) *A61P 25/30* (2006.01)
A61K 31/381 (2006.01) *A61P 3/04* (2006.01)
A61K 31/38 (2006.01)

(21) International Application Number:

PCT/EP2006/050444

(22) International Filing Date: 25 January 2006 (25.01.2006)

(25) Filing Language: English

(26) Publication Language: English

c/o Johnson & Johnson, Pharmaceutical, Research and Development, Poligono Industrial, Calle Jarama, 75 (ES).

(74) Common Representative: JANSSEN PHARMACEUTICA N.V.; Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(30) Priority Data:

05100547.8 27 January 2005 (27.01.2005) EP

(71) Applicant (*for all designated States except US*): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): CID-NÚÑEZ, José, Maria [ES/ES]; c/o Johnson & Johnson, Pharmaceutical, Research and Development, Poligono Industrial, Calle Jarama, 75 (ES). MEGENS, Antonius, Adrianus, Hendrikus, Petrus [NL/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). TRABANCO-SUÁREZ, Andrés, Avelino [ES/ES];

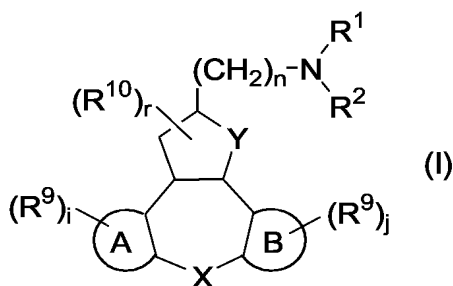
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROCYCLIC TETRACYCLIC TETRAHYDROFURAN DERIVATIVES AS 5HT₂ INHIBITORS IN THE TREATMENT OF CNS DISORDERS



(57) Abstract: This invention concerns novel substituted heterocyclic tetracyclic tetrahydrofuran derivatives with binding affinities towards serotonin receptors, in particular 5-HT_{2A} and 5-HT_{2C} receptors, and towards dopamine receptors, in particular dopamine D₂ receptors and with norepinephrine reuptake inhibition properties, pharmaceutical compositions comprising the compounds according to the invention, the use thereof as a medicine, in particular for the prevention and/or treatment of a range of psychiatric and neurological disorders, in particular certain psychotic, cardiovascular and gastrokinetic disorders and processes for their production. The compounds according to the invention can be represented by general Formula (I), and comprises also the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form thereof and prodrugs thereof, wherein all substituents are defined as in Claim 1.

WO 2006/079637 A1

HETEROCYCLIC TETRACYCLIC TETRAHYDROFURAN DERIVATIVES AS 5HT₂ INHIBITORS IN THE TREATMENT OF CNS DISORDERS

Field of the Invention

5

This invention concerns novel substituted heterocyclic tetracyclic tetrahydrofuran derivatives with binding affinities towards serotonin receptors, in particular 5-HT_{2A} and 5-HT_{2C} receptors, and towards dopamine receptors, in particular dopamine D₂ receptors and with norepinephrine reuptake inhibition properties, pharmaceutical compositions comprising the compounds according to the invention, the use thereof as a medicine, in particular for the prevention and/or treatment of a range of psychiatric and neurological disorders, in particular certain psychotic, cardiovascular and gastrokinetic disorders and processes for their production.

15

Background prior art

WO 97/38991, published October 23, 1997 (Janssen Pharmaceutica N.V.) discloses substituted tetracyclic tetrahydrofuran derivatives that may be used as therapeutic agents in the treatment or prevention of CNS disorders, cardiovascular disorders or gastrointestinal disorders. In particular, the compounds show affinity for the serotonin 5-HT₂ receptors, particularly for the 5-HT_{2A} and 5-HT_{2C}-receptors.

WO 99/19317, published April 22, 1999 (Janssen Pharmaceutica N.V.) discloses substituted tetracyclic tetrahydrofuran derivatives with a specific halogen substitution pattern on the dibenzoazepine, dibenzooxepine, dibenzothiepine or dibenzosuberane ring. The compounds are useful in the treatment or prevention of CNS disorders, cardiovascular disorders or gastrointestinal disorders and show a faster onset of action over the compounds as disclosed in WO 97/38991.

Both WO 03/048146 , published June 12, 2003 (Janssen Pharmaceutica N.V.) and WO 03/048147, published June 12, 2003 (Janssen Pharmaceutica N.V.) disclose processes for the preparation of each of the 4 diastereomers of cis-, respectively trans-fused 3,3a,8,12b-tetrahydro-2*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]furan derivatives in a stereochemically pure form from a single enantiomerically pure precursor.

35

WO 03/040122, published May 15, 2003 (Janssen Pharmaceutica N.V.) discloses mandelate salts of the compounds according to WO 97/38991 and WO 99/19317. Said

-2-

salts were surprisingly found to be more stable at enhanced temperature and relative humidity than the compounds disclosed in WO 97/38991 and WO 99/19317.

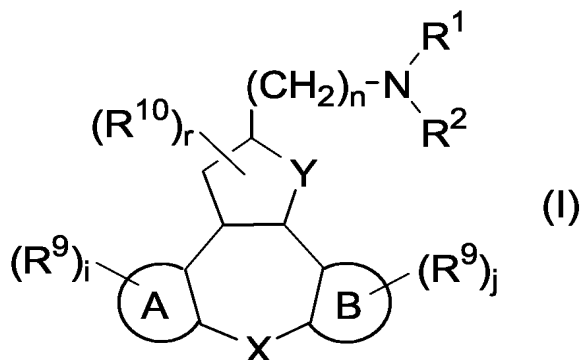
Further should be mentioned WP 97/39001, published October 23, 1997 (Janssen Pharmaceutica N.V.), which discloses heterocyclic tetracyclic isoxazolidine derivatives and which show affinity for the 5-HT₂ receptors.

Description of the Invention

It is the object of the present invention to provide novel heterocyclic analogues of the tetracyclic tetrahydrofuran derivatives of WO 97/38991 and WO 99/19317, which have been found to have surprising advantages over the latter compounds in regard to improved affinity for the 5-HT_{2A} and 5-HT_{2C} receptors and the norepinephrine reuptake transporters.

Surprisingly, the compounds of the present invention also showed a high to moderate dopamine D₂ activity, making the compounds interesting for the treatment of dopamine regulated conditions, in particular schizophrenia. None of the compounds of the prior art was documented to exhibit said dopamine D₂ activity and none of the prior art documents has pointed out how to introduce said activity in a molecule that has affinity for the 5-HT_{2A} and 5-HT_{2C} receptors, while retaining said affinity for the 5-HT_{2A} and 5-HT_{2C} receptors.

This goal is achieved by the present novel compounds according to Formula (I)



an *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

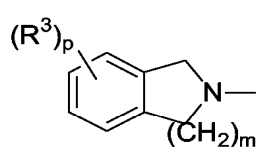
-3-

n is an integer, equal to zero ; 1 ; 2 ; 3 ; 4 ; 5 or 6 ;

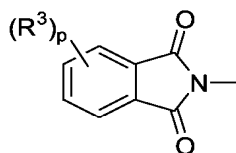
i, j are integers, independently from each other, equal to zero ; 1 ; 2 ; 3 or 4 ;

r is an integer, equal to zero ; 1 ; 2 ; 3 or 4 ;

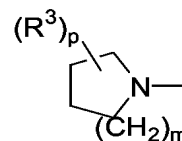
R¹ and R² each independently from each other, are hydrogen ; alkylcarbonyl ; alkyl ;
 5 alkyloxyalkyl ; alkylcarbonyloxyalkyl ; alkyloxycarbonylalkyl ; arylalkyl ;
 arylcarbonyl ; alkyloxycarbonyl ; aryloxycarbonyl ; arylalkylcarbonyl ; al-
 kyloxy-carbonylalkylcarbonyl ; mono- or di(alkyl)aminocarbonyl ; mono-
 or di(aryl)aminocarbonyl ; mono- or di(arylalkyl)aminocarbonyl ; mono- or
 di(alkyloxycarbonylalkyl)aminocarbonyl ; alkylsulphonyl ; arylsulphonyl ;
 10 arylalkylsulphonyl ; mono- or di(alkyl)aminothiocabonyl ; mono- or
 di(aryl)aminothiocabonyl ; mono- or di(arylalkyl)aminothiocabonyl ;
 mono-, di- or tri(alkyl)amidino ; mono-, di- or tri(aryl)amidino and mono-,
 di- or tri(arylalkyl)amidino ; or R¹ and R² taken together with the nitrogen
 atom to which they are attached may form a radical of Formula:



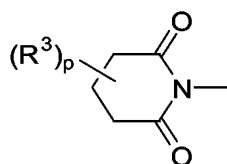
(a-1)



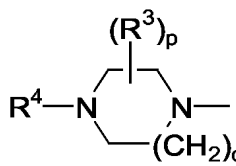
(a-2)



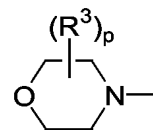
(a-3)



(a-4)



(a-5)



(a-6)

wherein :

p is an integer equal to zero ; 1 ; 2 ; 3 or 4 ;

q is an integer equal to 1 or 2 ;

m is an integer equal to zero ; 1 ; 2 or 3 ;

each R³ independently from each other, is selected from the group of
 halo ; hydroxy ; cyano ; alkyl ; alkyloxyalkyl ; aryloxyalkyl ; mono-
 or di(alkyl)aminoalkyl ; hydroxycarbonylalkyl ; alkyloxycarbonyl-
 alkyl ; mono- or di(alkyl)aminocarbonylalkyl ; mono- or di(aryl)-
 aminocarbonylalkyl ; mono- or di(alkyl)aminocarbonyloxyalkyl ; al-
 25 kyxycarbonyloxyalkyl ; arylaminocarbonyloxyalkyl ; arylalkylami-

5 nocarbonyloxyalkyl ; aryl ; alkyloxy ; aryloxy ; alkylcarbonyloxy ;
 arylcarbonyloxy ; arylalkylcarbonyloxy ; alkylcarbonyl ; arylcar-
 bonyl; aryloxy carbonyl ; hydroxycarbonyl ; alkyloxy carbonyl ;
 mono- or di-alkylamino ; alkylcarbonylamino ; arylalkylcarbonyl-
 amino ; arylcarbonylamino ; alkyloxy carbonylamino ; aminocarbon-
 ylamino ; mono- or di(arylalkyl)aminocarbonylamino ; alkylsulphon-
 ylalkylaminocarbonylamino ; or

two R³-radicals may form together a bivalent radical

- 10 -CR⁵R⁵-CR⁵R⁵-O- (b-1)
 -O-CR⁵R⁵-CR⁵R⁵- (b-2)
 -O-CR⁵R⁵-CR⁵R⁵-O- (b-3)
 -O-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵- (b-4)
 -CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-O- (b-5)
 -O-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-O- (b-6)
 15 -O-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵- (b-7)
 -CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-O- (b-8) and
 -O-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-O- (b-9)

wherein R⁵ is selected from the group of hydrogen ; halo ; hydroxy ;
 alkyloxy and alkyl ;

20 R⁴ is selected from the group of hydrogen ; alkyl ; arylalkyl ; alkyloxyal-
 kyl ; alkylcarbonyloxyalkyl ; alkyloxy carbonylalkyl ; arylcarbonylal-
 kyl ; alkylsulphonyloxyalkyl ; aryloxyaryl ; alkyloxy carbonylaryl ;
 alkylcarbonyl ; arylalkylcarbonyl ; alkyloxy carbonylalkylcarbonyl ;
 arylcarbonyl ; alkyloxy carbonyl ; aryloxy carbonyl ; arylalkyloxy car-
 25 bonyl ; mono- or di(alkyl)aminocarbonyl ; mono- or
 di(aryl)aminocarbonyl ; mono- or di(arylalkyl)aminocarbonyl ; mono-
 or di(alkyloxy carbonylalkyl)aminocarbonyl ; alkyloxyalkylaminocar-
 bonyl ; mono-, di- or tri(alkyl)amidino ; mono-, di- or
 tri(aryl)amidino ; mono-, di- or tri(arylalkyl)amidino ; alkylsulphonyl;
 30 arylalkylsulphonyl or arylsulphonyl ;

each R¹⁰ is independently from each other, alkyl or cyano ;

A and B are, each independently from each other, aryl or an heteroaryl radical fused
 to the central ring and selected from the group of furyl ; thienyl ; pyrrolyl ;
 oxazolyl ; thiazolyl ; imidazolyl ; isoxazolyl ; isothiazolyl ; oxadiazolyl ;
 35 triazolyl ; pyridinyl ; pyridazinyl ; pyrimidinyl ; pyrazinyl ; indolyl ; indol-
 izinyll ; isoindolyl ; benzofuryl ; isobenzofuryl ; benzothienyl ; indazolyl ;
 benzimidazolyl ; benzthiazolyl ; quinolizinyll ; quinolinyl ; isoquinolinyl ;

- phthalazinyl ; quinazolinyl ; quinoxalinyl ; chromenyl ; naphthyridinyl and naphthalenyl ; providing at least one of A and B is one of the above heteroaryl radicals ;
- each R⁹ is, independently from each other, selected from the group of hydrogen ;
- 5 halo ; cyano ; hydroxy ; carboxyl ; nitro ; amino ; mono- or di(alkyl)amino ; alkylcarbonylamino ; aminosulfonyl ; mono- or di(alkyl)aminosulfonyl ; alkyl ; alkenyl ; alkyloxy ; alkylcarbonyl and alkyloxycarbonyl ;
- Y represents O ; S ; S(=O) ; S(=O)₂ or NR⁸ ;
- X represents CR⁶R⁷ ; O ; S ; S(=O) ; S(=O)₂ or NR⁸ ; wherein
- 10 R6 and R7 each independently are selected from the group of hydrogen ; hydroxy ; alkyl and alkyloxy ; or
- R6 and R7 taken together may form a radical selected from the group of methylene (i.e. =CH₂) ; mono- or di(cyano)methylene ; a bivalent radical of Formula -(CH₂)₂- ; -(CH₂)₃- ; -(CH₂)₄- ; -(CH₂)₅- ; -O-(CH₂)₂-O- ;
- 15 -O(CH₂)₃O- ; or, together with the carbon atom to which they are attached, a carbonyl ;
- R⁸ is selected from the group of hydrogen ; alkyl ; alkylcarbonyl ; arylcarbonyl ; arylalkyl ; arylalkylcarbonyl ; alkylsulfonyl ; arylsulfonyl and arylalkylsulfonyl ;
- 20 aryl is phenyl or naphthyl, each optionally substituted with 1, 2 or 3 substituents selected from the group of halo ; nitro ; cyano ; hydroxy ; alkyloxy or alkyl ;
- alkyl represents a straight or branched saturated hydrocarbon radical having from 1 to 10 carbon atoms, a cyclic saturated hydrocarbon radical having from 3
- 25 to 8 carbon atoms or a saturated hydrocarbon radical containing a straight or branched moiety having from 1 to 10 carbon atoms and a cyclic moiety having from 3 to 8 carbon atoms ; each radical optionally substituted with one or more halo ; cyano ; oxo ; hydroxy ; formyl ; carboxyl or amino radicals ;
- 30 alkenyl represents a straight or branched unsaturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic unsaturated hydrocarbon radical having from 3 to 6 carbon atoms ; said radical having one or more double bonds and said radical being optionally substituted with one or more halo ; cyano ; oxo ; hydroxy ; formyl ; carboxyl or amino radicals ; and
- 35 halo represents fluoro ; chloro ; bromo and iodo.

The invention also relates to a compound according to the invention for use as a medicine.

5 The invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a therapeutically effective amount of a compound according to the invention.

10 The invention also relates to the use of a compound according to the invention for the preparation of a medicament for the prevention and/or treatment of conditions, either prophylactic or therapeutic or both, mediated through the 5-HT₂ and D₂ receptor, as well as the through norepinephrine reuptake inhibition.

15 In particular, the invention relates to the use of a compound according to the invention for the preparation of a medicament for the treatment and/or prevention of central nervous system disorders like anxiety, depression and mild depression, bipolar disorders, sleep- and sexual disorders, psychosis, borderline psychosis, schizophrenia, migraine, personality disorders or obsessive-compulsive disorders, social phobias or panic attacks, organic mental disorders, mental disorders in children, aggression, memory disorders and attitude disorders in older people, addiction, obesity, bulimia and similar
20 disorders.

More in particular, the invention relates to the use of a compound according to the invention for the preparation of a medicament for the treatment and/or prevention of anxiety, depression, psychosis, schizophrenia, migraine and addictive properties of
25 drugs of abuse.

Detailed description of the invention

30 In a preferred embodiment, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein R¹ and R² each, independently from each other, are hydrogen or alkyl, each alkyl radical optionally substituted with hydroxy ; or R¹ and R² taken together with the nitrogen atom to which they are attached, to form a radical of Formula (a-3) or
35 (a-5), wherein m = an integer, equal to 1 or 2. Preferably, alkyl is methyl or ethyl.

In a further preferred embodiment, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein A and B, each independently from each other, is aryl or an heteroaryl radical selected from thienyl and pyridinyl, providing that at least one of A and B is an heteroaryl radical. Preferably, A is a phenyl-moiety and the thienyl moiety is a thienyl moiety wherein S is at position 9 or 11.

In a further preferred embodiment, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein X is S, A is a phenyl-moiety and B is a thienyl moiety wherein S is at position 9 or 11. Most preferably, S is at position 9.

In a further preferred embodiment, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein Y is O.

In a further preferred embodiment, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein Y is CR⁶R⁷, O, S, S(=O), S(=O)₂ or NR⁸. Preferably, CR⁶R⁷ is CH₂. Preferably, NR⁸ is *N*-benzyl.

In a further preferred embodiment, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein :

- n is an integer equal to 1 ;
- i is an integer equal to 0 ;
- j is an integer equal to 0 or 1 ;
- r is an integer equal to 0 ;
- R¹ and R² are, each independently from each other, hydrogen, methyl, ethyl, or hydroxyethyl ;
- A is phenyl ;
- B is thienyl or pyridinyl

R⁹ is hydrogen ;
R¹⁰ is hydrogen, hydroxymethyl, methoxycarbonyl or ethoxycarbonyl ;
Y is O ;
X is CH₂, S or *N*-benzyl.

5

In the framework of this application, alkyl is defined as a monovalent straight or branched saturated hydrocarbon radical having from 1 to 10 carbon atoms, for example methyl, ethyl, propyl, butyl, 1-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl ; alkyl further defines a monovalent cyclic saturated hydrocarbon radical having from 3 to 8
10 carbon atoms, for example cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The definition of alkyl also comprises an alkyl radical that is optionally substituted on one or more carbon atoms with one or more phenyl, halo, cyano, oxo, hydroxy, formyl and amino radicals, for example hydroxyalkyl, in particular hydroxymethyl and hydroxyethyl and polyhaloalkyl, in particular difluoromethyl and
15 trifluoromethyl.

In the framework of this application, alkenyl is defined as an alkyl radical as defined above further comprising one or more double bonds, for example ethenyl, propenyl, butenyl, pentenyl, hexenyl, cyclopropenyl, methylcyclopropenyl, cyclobutenyl,
20 cyclopentenyl and cyclohexenyl. The definition of alkenyl also comprises an alkenyl radical that is optionally substituted on one or more carbon atoms with one or more phenyl, halo, cyano, oxo, hydroxy, formyl and amino radicals, for example hydroxyalkenyl, in particular hydroxyethenyl.

25 In the framework of this application, halo is generic to fluoro, chloro, bromo and iodo.

In the framework of this application, with "compounds according to the invention" is meant a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the
30 *N*-oxide form thereof and a prodrug thereof.

In the framework of this application, with "compounds according to the invention" is meant a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the
35 *N*-oxide form thereof and a prodrug thereof.

In the framework of this application, an element, in particular when mentioned in relation to a compound according to Formula (I), comprises all isotopes and isotopic mixtures of this element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. In particular, when hydrogen is mentioned, it is understood to refer to ^1H , ^2H , ^3H and mixtures thereof; when carbon is mentioned, it is understood to refer to ^{11}C , ^{12}C , ^{13}C , ^{14}C and mixtures thereof; when nitrogen is mentioned, it is understood to refer to ^{13}N , ^{14}N , ^{15}N and mixtures thereof; when oxygen is mentioned, it is understood to refer to ^{14}O , ^{15}O , ^{16}O , ^{17}O , ^{18}O and mixtures thereof; and when fluor is mentioned, it is understood to refer to ^{18}F , ^{19}F and mixtures thereof.

The compounds according to the invention therefore also comprise compounds with one or more isotopes of one or more element, and mixtures thereof, including radioactive compounds, also called radiolabelled compounds, wherein one or more non-radioactive atoms has been replaced by one of its radioactive isotopes. By the term "radiolabelled compound" is meant any compound according to Formula (I), an *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, which contains at least one radioactive atom. For example, compounds can be labelled with positron or with gamma emitting radioactive isotopes. For radioligand-binding techniques (membrane receptor assay), the ^3H -atom or the ^{125}I -atom is the atom of choice to be replaced. For imaging, the most commonly used positron emitting (PET) radioactive isotopes are ^{11}C , ^{18}F , ^{15}O and ^{13}N , all of which are accelerator produced and have half-lives of 20, 100, 2 and 10 minutes respectively. Since the half-lives of these radioactive isotopes are so short, it is only feasible to use them at institutions which have an accelerator on site for their production, thus limiting their use. The most widely used of these are ^{18}F , $^{99\text{m}}\text{Tc}$, ^{201}Tl and ^{123}I . The handling of these radioactive isotopes, their production, isolation and incorporation in a molecule are known to the skilled person.

In particular, the radioactive atom is selected from the group of hydrogen, carbon, nitrogen, sulfur, oxygen and halogen. Preferably, the radioactive atom is selected from the group of hydrogen, carbon and halogen.

In particular, the radioactive isotope is selected from the group of ^3H , ^{11}C , ^{18}F , ^{122}I , ^{123}I , ^{125}I , ^{131}I , ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br . Preferably, the radioactive isotope is selected from the group of ^3H , ^{11}C and ^{18}F .

The pharmaceutically acceptable salts are defined to comprise the therapeutically active non-toxic acid addition salts forms that the compounds according to Formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicylic acid, p-aminosalicylic acid, pamoic acid and mandelic acid.

Conversely said acid addition salt forms can be converted into the free base form by treatment with an appropriate base .

The compounds according to Formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salts forms by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said salts forms can be converted into the free forms by treatment with an appropriate acid.

Quaternary ammonium salts of compounds according to Formula (I) defines said compounds which are able to form by a reaction between a basic nitrogen of a compound according to Formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, in particular methyl iodide and benzyl iodide. Other reactants with good leaving groups may also be used, such as, for example, alkyl trifluoromethanesulfonates, alkyl methanesulfonates and alkyl p-toluenesulfonates. A quaternary ammonium salt has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate ions.

The term addition salt as used in the framework of this application also comprises the solvates that the compounds according to Formula (I) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

- 5 The *N*-oxide forms of the compounds according to Formula (I) are meant to comprise those compounds of Formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more tertiary nitrogens (e.g. of the piperazinyll or piperidinyll radical) are *N*-oxidized. Such *N*-oxides can easily be obtained by a skilled person without any inventive skills and
10 they are obvious alternatives for the compounds according to Formula (I) since these compounds are metabolites, which are formed by oxidation in the human body upon uptake. As is generally known, oxidation is normally the first step involved in drug metabolism (Textbook of Organic Medicinal and Pharmaceutical Chemistry, 1977, pages 70- 75). As is also generally known, the metabolite form of a compound can
15 also be administered to a human instead of the compound per se, with much the same effects.

- The compounds according to the invention may possess at least one oxidizable nitrogen (i.e. the tertiary amines moiety in the case R^1 and R^2 are both not equal to H). In which
20 case, it is highly likely that *N*-oxides are formed in the human metabolism.

- The compounds of Formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting
25 material of Formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g.
30 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

- 35 The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise

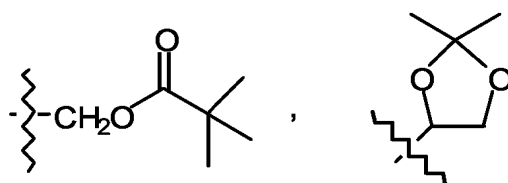
mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of Formula (I) are obviously intended to be embraced within the scope of this invention.

Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. *R** and *S** each indicate optically pure stereogenic centers with undetermined absolute configuration. If “ α ” and “ β ” are used : the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the “ α ” position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system (hydrogen atom in compounds according to Formula (I)) relative to the position of the highest priority substituent on the reference atom is denominated “ α ”, if it is on the same side of the mean plane determined by the ring system, or “ β ”, if it is on the other side of the mean plane determined by the ring system.

The compounds of Formula (I) have at least one asymmetric center at the carbon atom in the five membered ring attached to the alkylamino side chain. Said asymmetric center and any other asymmetric center which may be present (e.g. certain X groups) , are indicated by the descriptors R and S.

The invention also comprises derivative compounds (usually called “pro-drugs”) of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, “Prodrugs”, *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, **29**, pp. 455-473.

- Pro-drugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the
- 5 *N*-oxide form thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the Formula—COOR^x, where R^x is a C₁₋₆alkyl, phenyl, benzyl or one of the following groups :



- 10 Amidated groups include groups of the Formula— CONR^yR^z, wherein R^y is H, C₁₋₆alkyl, phenyl or benzyl and R^z is —OH, H, C₁₋₆alkyl, phenyl or benzyl. Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

15

Pharmacology

- The compounds of the present invention, in particular compounds according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof,
- 20 show affinity for 5-HT₂ receptors, particularly for 5-HT_{2A} and 5-HT_{2C} receptors (nomenclature as described by D. Hoyer in "Serotonin (5-HT) in neurologic and psychiatric disorders" edited by M.D. Ferrari and published in 1994 by the Boerhaave Commission of the University of Leiden) and affinity for the D₂ receptor as well as norepinephrine reuptake inhibition activity. The serotonin antagonistic properties of the present compounds
- 25 may be demonstrated by their inhibitory effect in the "5-hydroxytryptophan Test on Rats" which is described in Drug Dev. Res., 13, 237-244 (1988).

- The compounds of the present invention, in particular compounds according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof also have favourable physicochemical properties. For instance, they are chemically stable compounds.
- 30

In view of their capability to block 5-HT₂ receptors, and in particular to block 5-HT_{2A} and 5-HT_{2C} receptors, as well as the D₂ receptor and by also effecting the norepinephrine reuptake inhibition activity, the compounds of the present invention, in particular compounds according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, are useful as a medicine, in particular in the prophylactic and therapeutic treatment of conditions mediated through these receptors.

10 The invention therefore relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, for use as a medicine.

15 The invention also relates to the use of a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof for the manufacture of a medicament for the prevention and/or treatment of conditions mediated through the 5HT₂ receptor, in particular 5HT_{2A} and 5HT_{2C} receptor and D₂ receptor, as well as the through norepinephrine reuptake inhibition.

In view of these pharmacological and physicochemical properties, the compounds according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, are useful as therapeutic agents in the treatment and/or the prevention of central nervous system disorders like anxiety ; depression and mild depression ; bipolar disorders including bipolar mania and depression ; sleep- and sexual disorders ; psychosis ; borderline psychosis ; schizophrenia ; migraine ; personality disorders ; obsessive-compulsive disorders ; social phobias ; panic attacks ; attention disorders including attention deficit hyperactivity disorder (ADHD) ; organic mental disorders ; mental disorders in children such as ADHD ; aggression ; memory disorders and attitude disorders, especially in older people ; addiction ; obesity ; bulimia and similar disorders.

35 In particular, the present compounds may be used as anxiolytics, antidepressants, antipsychotics, anti-schizophrenia agents, anti-migraine agents and as agents having the potential to overrule the addictive properties of drugs of abuse.

The compounds of the present invention, in particular compounds according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof may also be used as therapeutic agents in the treatment of motoric disorders. It may be advantageous to use the present compounds in combination with classical therapeutic agents for such disorders.

The compounds of the present invention, in particular compounds according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, may also serve in the treatment or the prevention of damage to the nervous system caused by trauma, stroke, neurodegenerative illnesses, cognitive disorders such as dementia and Alzheimers disease and the like; cardiovascular disorders like high blood pressure, thrombosis, stroke, and the like; and gastrointestinal disorders like dysfunction of the motility of the gastrointestinal system and the like.

In view of the above uses, it follows that the present invention also provides a method of treating warm-blooded animals suffering from such diseases, said method comprising the systemic administration of a therapeutic amount of a compounds of the present invention, in particular compounds according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, effective in treating the above described disorders, in particular, in treating anxiety, psychosis, depression, bipolar disorders including bipolar depression, migraine and addictive properties of drugs of abuse.

The present invention thus also relates to compounds of the present invention, in particular compounds according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof for use as a medicine, in particular, the compounds of Formula (I) may be used for the manufacture of a medicament for treating anxiety, psychosis, depression, bipolar disorders including bipolar depression, migraine and addictive properties of drugs of abuse.

Those of skill in the treatment of such diseases could determine the effective therapeutic daily amount from the test results presented hereinafter. An effective therapeutic

daily amount would be from about 0.01 mg/kg to about 10 mg/kg body weight, more preferably from about 0.05 mg/kg to about 1 mg/kg body weight.

5 The invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention, in particular a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof.

10 The compounds according to the invention, in particular the compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and the prodrugs thereof, or any subgroup or combination thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may
15 be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form
20 suitable, in particular, for administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the
25 case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may
30 be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing

agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may
5 be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage
10 form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspen-
15 sions and the like, and segregated multiples thereof.

Since the compounds according to the invention are potent orally administrable compounds, pharmaceutical compositions comprising said compounds for administration orally are especially advantageous.

20 In order to enhance the solubility and/or the stability of the compounds of Formula (I) in pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl- β -cyclodextrin. Also co-solvents such as alcohols may improve
25 the solubility and/or the stability of the compounds according to the invention in pharmaceutical compositions.

Preparation

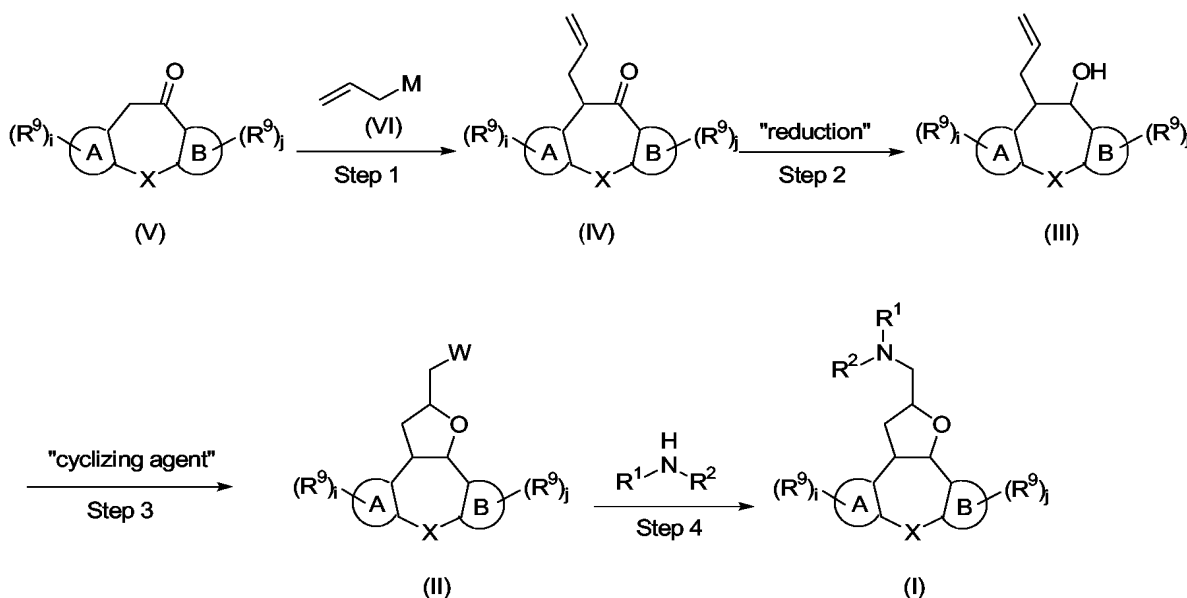
30 The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person.

The compounds of Formula (I) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers that can be separated from
35 one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently sepa-

rated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

Suitable preparation schemes for the compounds of the invention include the following:

Scheme A



Step 1: Reaction of an intermediate compound according to Formula (V) with a reagent of Formula (VI). This reaction can be performed by any one of the art-known procedures for alkylation of ketones in position α under acidic or basic reaction conditions (for example the reaction can be done in an organic solvent such as tetrahydrofuran, with a base such as, for example, sodium hydride or lithium *N,N*-diisopropylamine and using allyl bromide as the alkylating agent) and yields an intermediate compound according to Formula (IV) wherein R^9 , i , j , ring A, ring B and X all have the meaning as described above for a final compound according to Formula (I). For a compound according to Formula (VI), M is a suitable group for an alkylation reaction, such as, for example halo, hydroxy or acetoxy.

Step 2: Reduction of a compound according to Formula (IV) for example with sodium borohydride in an organic solvent such as tetrahydrofuran or methanol, typically at room temperature, to yield a compound according to Formula (III).

5

Step 3: Reaction of an intermediate compound according to Formula (III) with a cyclizing agent, such as, for example, iodine together with sodium hydrogencarbonate, in an organic solvent, such as, for example acetonitrile or dichloromethane, yields an intermediate compound according to Formula (II), which is novel, wherein W represents a
10 suitable leaving group, preferably a halo, alkyl- or arylsulphonyloxy, in particular 4-(methylphenyl)sulphonyloxy or iodo.

Step 4: *N*-alkylation of an intermediate compound according to Formula (II) with an amine of Formula HNR^1R^2 , wherein R^1 and R^2 are defined as in Formula (I), by any of
15 the art-known procedures, yields a final compound according to Formula (I), which is novel. For instance, said *N*-alkylation can conveniently be carried out as described in WO 97/38991 in a reaction-inert solvent such as, for example, methanol, methylisobutyl ketone, *N,N*-dimethylformamide or dimethylsulfoxide, and optionally in the presence of a suitable base. Stirring and elevated temperatures, for instance reflux temperature,
20 may enhance the rate of the reaction. Typical reaction conditions are 8 hours at 130°C.

Alternatively, said *N*-alkylation may also be performed using the procedure described by Monkovic et al. (J. Med. Chem. (1973), 16(4), p. 403-407) which involves the use
25 of a pressurised reaction vessel.

Alternatively, said *N*-alkylation may also be performed by heating at high temperature, for example 120 °C, an intermediate compound according to Formula (II), an amine of Formula NHR^1R^2 and a base, for example calcium oxide, in an organic solvent such as
30 THF, in a pressurised reaction vessel.

The compounds of Formula (I) may also be converted into each other following art-known transformation reactions. For instance,

a) a compound according to Formula (I), wherein R^1 and R^2 taken together with the
35 nitrogen atom to which they are attached form a radical of Formula (b), may be converted into the corresponding primary amine by treatment with hydrazine or aqueous alkali;

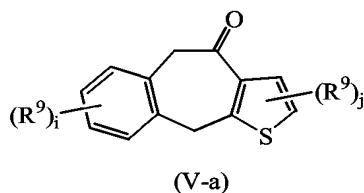
-20-

- b) a compound according to Formula (I), wherein R^1 or R^2 is trifluoromethylcarbonyl, may be converted into the corresponding primary or secondary amine by hydrolysis with aqueous alkali;
- c) a compound according to Formula (I), wherein R^1 or R^2 is C_{1-6} alkyl substituted with C_{1-6} alkylcarbonyloxy may be hydrolyzed into a compound according to Formula (I) wherein R^1 or R^2 is C_{1-6} alkyl substituted with hydroxy;
- d) a compound according to Formula (I), wherein R^1 and R^2 are both hydrogen may be mono- or di-*N*-alkylated to the corresponding amine form;
- e) a compound according to Formula (I), wherein R^1 and R^2 are both hydrogen, or R^1 or R^2 is hydrogen, may be *N*-acylated to the corresponding amide;
- f) a compound according to Formula (I), containing a C_{1-6} alkyloxycarbonyl group may be hydrolyzed to the corresponding carboxylic acid;
- g) a compound according to Formula (I) in which R^9 is hydrogen, i.e. *i* and/or *j* is zero, can be converted to a corresponding alkyloxycarbonyl compound by treatment with an appropriate acylating agent, e.g. the appropriate alkyloxycarbonyl chloride in the presence of butyllithium in hexane using an organic solvent such as tetrahydrofuran; or
- h) a compound according to Formula (I) in which R^9 is alkyloxycarbonyl can be converted to a corresponding hydroxymethyl compound by reduction for example with $LiAlH_4$ for example in an organic solvent such as tetrahydrofuran.

The intermediate compounds mentioned hereinabove are either commercially available or may be made following art-known procedures. For instance, intermediate compounds of Formula (II) may be prepared according to the procedure described by Monkovic et al. (J. Med. Chem. (1973), 16(4), p. 403-407).

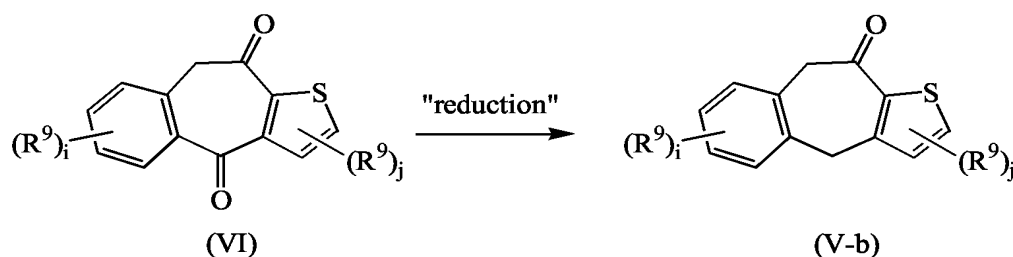
The intermediate compounds of Formula (V) in which X is CH_2 , A is a phenyl group and B is a thienyl group, represented by Formula (V-a) below, are commercially available or may be made following art-known procedures. For instance, intermediate compounds of Formula (V-a) may be prepared according to the procedure described by Protiva et al. (Collection of Czechoslovak Chemical Communications 1969, 34(2), 468-478).

-21-

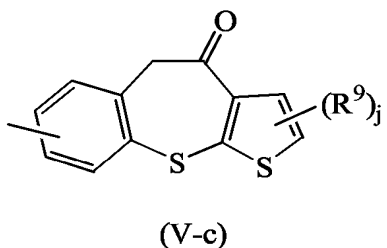


The intermediate compounds of Formula (V) in which X is S, A is a phenyl group and B is a thienyl group, represented by Formula (V-b) below, may be prepared by reduction of an intermediate compound according to Formula (VI) with a suitable reducing agent, such as aluminium hydride, in an organic solvent such as, for example, tetrahydrofuran.

Scheme B

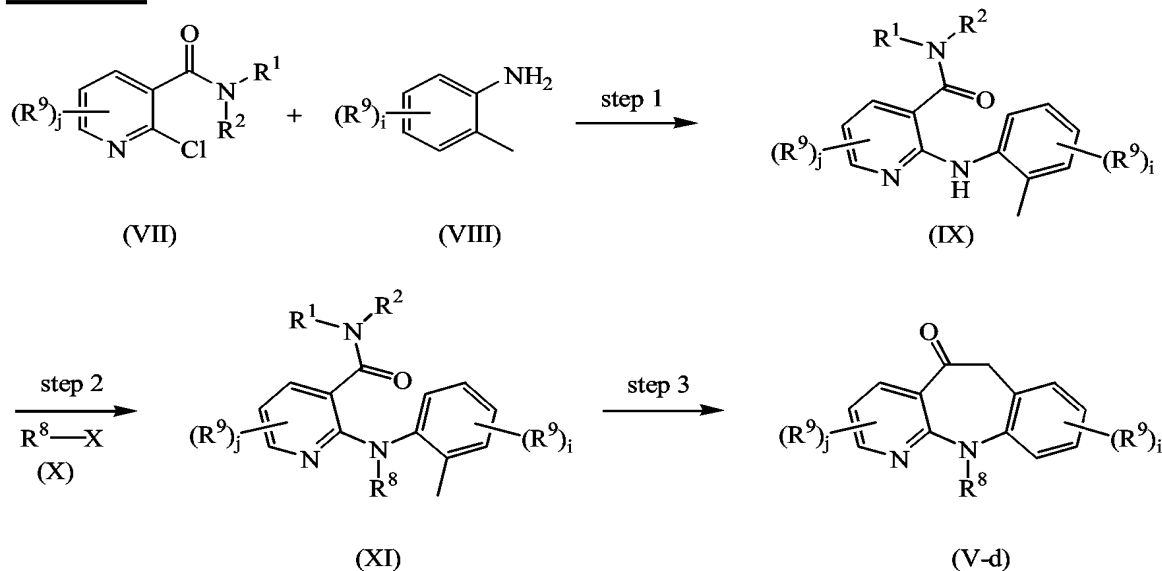


An intermediate compound according to Formula (VI) may be prepared by the procedures described by Michal Majchrzak (Journal of Heterocyclic Chemistry 1985, 22(5), 1203-4 ; Journal of Heterocyclic Chemistry 1985, 22(5), 1205-6) and in patent publications DE2625642 and PL158223. The intermediate compounds of Formula (V) in which X is S, A is a phenyl group and B is a thienyl group, represented by Formula (V-c) below, are commercially available or may be made following art-known procedures. For instance, intermediate compounds of Formula (V-c) may be prepared according to the procedures described in patent publications CS142473, CS217949 and/or CS200271.



The intermediate compounds of Formula (V) in which X is NR^8 , A is a phenyl group and B is a pyridinyl group, represented by Formula (V-d) below, may be prepared according to the reaction sequence shown in Scheme C.

5 **Scheme C**



Step 1: Reaction of a compound according to Formula (VII) with a compound according to Formula (VIII) at high temperature, such as for example 200 °C to give an intermediate compound according to Formula (IX) wherein R^1 , R^2 , R^9 , i, j, have the meanings as described above for the final compound according to Formula (I).

Step2: Reaction of a compound according to Formula (IX) with a compound according to Formula (X) in the presence of a base, such as for example sodium hydride, in an organic solvent such as for example *N,N*-dimethylformamide. Alternatively, the reaction can be carried out by any of the art-known procedures for the alkylation of aniline derivatives. For a compound according to Formula (X), X is a suitable group for an alkylation reaction, such as, for example halo, hydroxy or acetoxy and R^8 has the meaning as described above for the final compound according to Formula (I).

Step3: Cyclization of an intermediate compound according to Formula (XI) gives a compound according to Formula (V-d) wherein R^8 , R^9 , i, j, have the meanings as described above for the final compound according to Formula (I). The cyclization reaction can be effected by art-known procedures, such as the procedure described by Lohse et al. (Tetrahedron Letters, 2001, 42, 385-389).

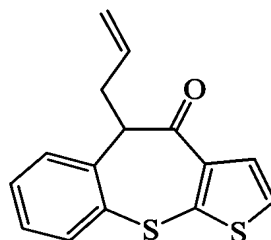
Pure stereochemically isomeric forms of the compounds of Formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

The compounds of Formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid respectively with a suitable chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The following examples are intended to illustrate and not to limit the scope of the present invention.

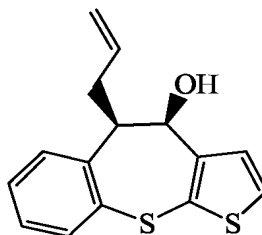
Experimental part

Hereinafter, "DCM" is defined as dichloromethane; "THF" is defined as tetrahydrofuran; "BuLi" is defined as n-butyl-lithium; "EtOAc" is defined as ethyl acetate; and "MeOH" is defined as methanol.

A. Preparation of the intermediate compoundsExample A1a) Preparation of intermediate compound 1

racemic mixture

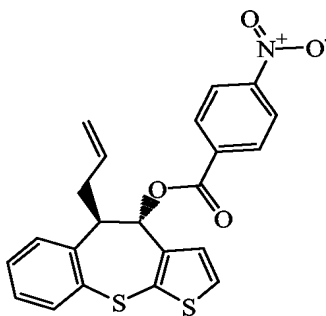
Reaction under N₂ atmosphere: a solution of thieno[2,3-b][1]benzothiepin-4(5H)-one (0.03998 mol) in THF dry (750 ml) was cooled to 0 °C and then sodium hydride 60% in mineral oil (0.040 mol) was added portionwise. The reaction mixture was stirred for 45 min. at 0 °C, then at room temperature for 1 hour. After cooling to 0 °C, a mixture of 3-bromo-1-propene (0.40 mol) in THF dry (250 ml) was added dropwise and the resulting mixture allowed to reach room temperature overnight. Water was added and the organic solvent was evaporated. The aqueous concentrate was extracted two times with DCM; the organic layers were combined, dried (Na₂SO₄) and the solvent was evaporated (vac.), yielding 10.22 g of **intermediate compound 1**.

b) Preparation of intermediate compound 2racemic mixture of *cis/trans* diastereoisomers 90/10

A solution of **intermediate compound 1** (0.03744 mol) in THF (200 ml) was cooled to 0°C and sodium tetrahydroborate (0.045 mol) was added portionwise. After 10 min., MeOH (100 ml) was added dropwise, the reaction mixture was warmed to room temperature and stirred further overnight. The mixture was quenched with a saturated aqueous ammonium chloride solution. and the organic solvent was evaporated (vac.). The aqueous concentrate was extracted two times with DCM; the organic layers were combined, washed with brine and with water, then dried (Na₂SO₄). The solvent was evaporated (vac.) and the residue was purified by short open column chromatography. The product fractions were collected and the solvent was evaporated, yielding (mixture of isomers: *cis/trans* 90/10) **intermediate compound 2**.

-25-

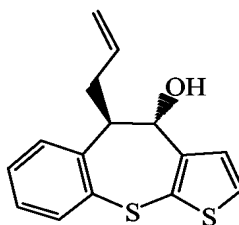
c) Preparation of intermediate compound 3



racemic mixture

A solution of triphenyl-phosphine (0.073 mol) in THF (q.s.) was stirred under N₂ at 0°C, bis(1-methylethyl) diazenedicarboxylate (0.071 mol) was added and the resulting suspension was stirred for 0.5 hour. A solution of **intermediate compound 2** (0.036 mol) and 4-nitro-benzoic acid (0.073 mol) in THF (q.s.) was added dropwise, the reaction mixture was gradually warmed to room temperature and stirred for 16 hours. The solvent was evaporated and the residue was dissolved in DCM, washed with water and with brine, then dried (Na₂SO₄). The solvent was evaporated and the residue was purified by preparative high-performance liquid chromatography (eluent: EtOAc/Heptane 2/8). The pure fractions were collected and the solvents was evaporated, yielding **intermediate compound 3**.

d) Preparation of intermediate compound 4

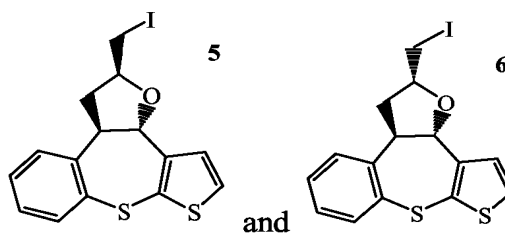


racemic mixture

A mixture of **intermediate compound 3** (0.018 mol) was stirred in THF (200 ml) at 0°C and then a mixture of lithium hydroxide (0.020 mol) in water (50 ml) was added dropwise. The reaction mixture was allowed to reach room temperature for 16 hours and the organic solvent was evaporated. The aqueous concentrate was washed with DCM; the organic layer was separated, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure, yielding 5.43 g of **intermediate compound 4**.

-26-

e) Preparation of intermediate compounds 5 and 6



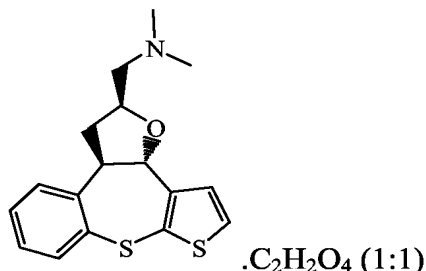
intermediate compound 5 [2RS-(2 β , 3 α , 11 β)] and
intermediate compound 6 [2RS-(2 α , 3 α , 11 β)]

5 Bis(pyridine)iodinium tetrafluoroborate (0.0186 mol) was added portionwise to a mixture of **intermediate compound 4** (0.0169 mol) in DCM (q.s.) at room temperature under N₂ atmosphere and the resulting solution was stirred for 1 hour, then a sodium thiosulfate aqueous solution was added. The organic layer was separated, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified by preparative, high-performance liquid chromatography. Two product fractions were collected and the solvents were evaporated, yielding 2.5 g of **intermediate compound 5** and 2.1 g of **intermediate compound 6**.

10 B. Preparation of the final compounds

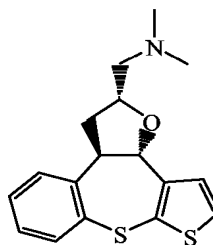
Example B1

Preparation of final compound 1
(free base) and 2

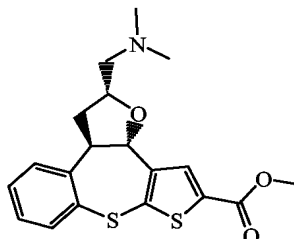


15 A mixture of **intermediate compound 5** (0.00127 mol), dimethylamine (0.020 mol, 2M in THF) and calcium oxide (0.100 g) in THF (10 ml) was heated at 120 °C (oil bath temperature) into a Parr reactor vessel for 8 hours and then the reaction mixture was cooled to room temperature. The solids were filtered off and the organic solvent was evaporated. The residue thus obtained was purified in a manifold (vac.) using a Sep-Pak silica cartridge (eluent: DCM/(MeOH/NH₃) mixtures). The product fractions were collected and the solvent was evaporated to yield compound 1, namely the **free base of compound 2**. The residue was converted into the ethanedioic acid salt by treatment
 20 with ethanedioic acid in diethyl ether. The resulting precipitate was filtered off, washed with cold diethylether and dried, yielding **final compound 2** (mixture of diastereoisomers 80/20).

-27-

Example B2Preparation of compound 3

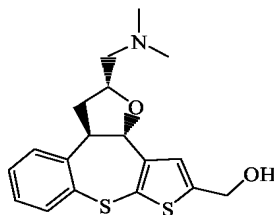
A mixture of **intermediate compound 6** (0.00145 mol), dimethylamine 2M in THF (0.020 mol) and calcium oxide (0.200 g) in THF (20 ml) was heated in a Parr reactor vessel for 10 hours at 120 °C (oil bath temperature), then the reaction mixture was cooled to room temperature and the solids were filtered off. The organic solvent was evaporated and the residue thus obtained was taken up in DCM and washed with a saturated aqueous NaHCO₃ solution. The organic layer was separated, dried (Na₂SO₄), filtered off and the solvent was evaporated. The residual oil was purified in a manifold (vac.) using a Sep-Pak silica cartridge (eluent: DCM/(MeOH/NH₃)). The product fractions were collected and the solvent was evaporated, yielding **final compound 3**.

Example B3Preparation of final compound 4

Reaction under N₂ atmosphere: a solution of **final compound 3** (0.00104 mol) in THF dry (15 ml) was cooled to -78 °C and then BuLi 1.6M in hexane (0.0011 mol) was added dropwise. The reaction mixture was stirred at -78 °C for 35 min. and dimethyl carbonate (0.003 mol) was added. The resulting mixture was allowed to reach room temperature in 1 hour, water was added and the organic layer was evaporated. The residue thus obtained was taken up in DCM and washed with a saturated aqueous NaHCO₃ solution. The organic layer was separated, dried (Na₂SO₄), filtered off and the solvent was evaporated. The resulting residue was purified in a manifold (vac.) using a Sep-Pak silica cartridge. The product fractions were collected and the solvent was evaporated. The residue was further purified by high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding **final compound 4**.

25

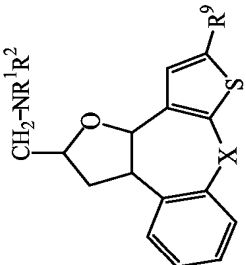
-28-

Example B4Preparation of final compound 5

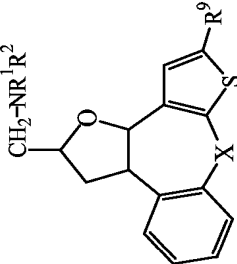
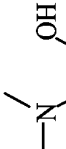
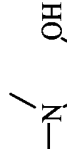
A mixture of **final compound 4** (0.0004 mol) in THF (q.s.) was stirred at room temperature under N₂ and lithium tetrahydroaluminate (0.00044 mol) was added, then the reaction mixture was stirred for 2 hours and an aqueous saturated ammonium chloride solution was added. The organic layer was separated, dried (MgSO₄), filtered off and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: DCM/MeOH 97/3). The product fractions were collected and the solvent was evaporated, yield 0.153 g of **final compound 5**.

10

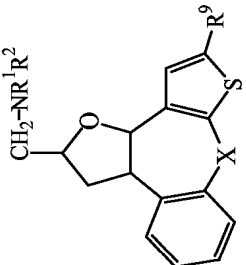
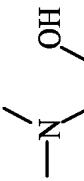
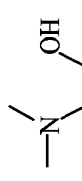
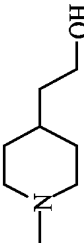
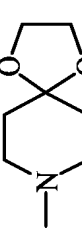
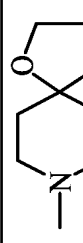
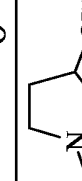
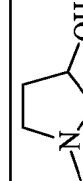
Table 1

					
Co. No.	Ex. No.	-NR ¹ R ²	R ⁹	X	Physical data
6	B1	-NHCH ₃	-H	-CH ₂ -	mixture of four diastereoisomers not assigned ; oxalate (1:1)
7	B1	-NHCH ₃	-H	-CH ₂ -	mixture (83:6:6:5) of four diastereoisomers (83) [2RS-(2α, 3αβ, 11bα)]; other diastereoisomers not assigned ; oxalate (1:1)
8	B1	-NHCH ₃	-H	-CH ₂ -	mixture (62:25:10:3) of four diastereoisomers (62) [2RS-(2β, 3αβ, 11bα)]; (25) [2RS-(2α, 3αα, 11bα)]; (10) [2RS-(2α, 3αβ, 11bα)]; (3) [2RS-(2β, 3αα, 11bα)] ; oxalate (1:1)
33	B1	-N(CH ₃) ₂	-H	-CH ₂ -	mixture (95.5:4.5) of two <i>trans</i> fused diastereoisomers (95.5) [2RS-(2α, 3αβ, 11bα)]: (4.5) [2RS-(2β, 3αβ, 11bα)]; oxalate (1: 1) ; m.p. = 228.4 °C
20	B1	-NHCH ₃	-H	-S-	[2RS-(2α, 3αα, 11bβ)] ; oxalate (1:1)
21	B1	-NHCH ₃	-H	-S-	[2RS-(2β, 3αα, 11bβ)] oxalate (1:1)
22	B1	-NHCH ₃	-H	-S-	[2RS-(2β, 3αα, 11bβ)]

-30-

					
Co. No.	Ex. No.	-NR ¹ R ²	R ⁹	X	Physical data
31	B1	-NHCH ₃	-H	-S-	[2S*-(2β, 3αβ, 11bα)] oxalate (1:1)
32	B1	-NHCH ₃	-H	-S-	[2RS-(2α, 3αα, 11bβ)] oxalate (1:1)
9	B1	-N(CH ₃) ₂	-H	-S-	mixture of three racemic diastereoisomers: 63% [2RS-(2α, 3αβ, 12bα)]; 28% [2RS-(2α, 3αβ, 12bβ)]; 9% not assigned ; oxalate (1:1)
14	B1	-N(CH ₃) ₂	-H	-S-	[2RS-(2α, 3αα, 11bα)] oxalate (1:1)
19	B2	-N(CH ₃) ₂	-H	-S-	[2RS-(2α, 3αα, 11bβ)] oxalate (1:1)
1	B1	-N(CH ₃) ₂	-H	-S-	[2RS-(2β, 3αα, 11bβ)]
2	B1	-N(CH ₃) ₂	-H	-S-	[2RS-(2β, 3αα, 11bβ)] ; oxalate (1:1) ; m.p. = 215.4 °C
3	B2	-N(CH ₃) ₂	-H	-S-	[2RS-(2α, 3αα, 11bβ)]
10	B1		-H	-S-	[2RS-(2α, 3αβ, 11bα)] oxalate (1:1); m.p. = 84.8 °C
18	B1		-H	-S-	[2RS-(2α, 3αα, 11bβ)] oxalate (1:1)

-31-

<div><div>CH₂-NR¹R²</div><div></div></div>						Co. No.	Ex. No.	-NR ¹ R ²	R ⁹	X	Physical data
25	B1			-H	-S-	mixture (75:25) of two <i>trans</i> fused diastereoisomers (75) [2RS-(2α, 3αβ, 11bα)]: (25) [2RS-(2β, 3αβ, 11bα)]					
26	B1			-H	-S-	mixture (75:25) of two <i>trans</i> fused diastereoisomers (75) [2RS-(2α, 3αβ, 11bα)]: (25) [2RS-(2β, 3αβ, 11bα)]					
11	B1			-H	-S-	mixture of two diastereoisomers; major component: [2RS-(2α, 3αβ, 11bα)] ;oxalate (1:1) ; m.p. = 131.2 °C					
13	B1			-H	-S-	[2RS-(2α, 3αβ, 11bα)]; oxalate (1:1) ; m.p. = 131.7 °C					
17	B1			-H	-S-	[2RS-(2α, 3αα, 11bβ)] oxalate (1:1)					
16	B1			-H	-S-	{2RS-[2α(3'RS), 3αα, 11bβ]} oxalate (1:1)					
23	B1			-H	-S-	{2RS-[2β(3'RS), 3αα, 11bβ]} oxalate (1:1)					

-32-

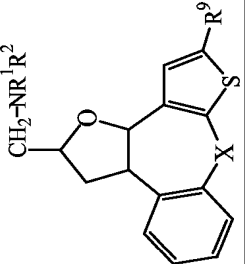
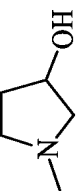
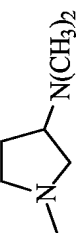
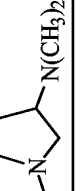
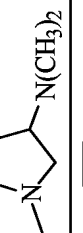
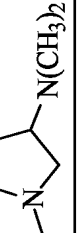
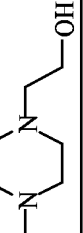
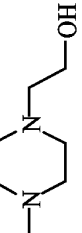
					
Co. No.	Ex. No.	-NR ¹ R ²	R ⁹	X	Physical data
24	B1		-H	-S-	{2RS-[2β(3'RS), 3αα, 11bβ]}
27	B1		-H	-S-	{2RS-[2α(3'RS), 3αα, 11bβ]} oxalate (1:1)
28	B1		-H	-S-	{2RS-[2α(3'RS), 3αα, 11bβ]}
29	B1		-H	-S-	{2RS-[2β(3'RS), 3αα, 11bβ]} oxalate (1:1)
30	B1		-H	-S-	{2RS-[2β(3'RS), 3αα, 11bβ]}
12	B1		-H	-S-	[2RS-(2α, 3αβ, 11bα)] ; oxalate (1:1) ; m.p. = 224.6 °C
15	B1		-H	-S-	[2RS-(2α, 3αα, 11bβ)] oxalate (1:1)
34	B1	-N(CH ₃) ₂	-COOCH ₂ CH ₃	-S-	[2RS-(2β, 3αα, 11bα)] oxalate (1:1); m.p. = 188.9 °C
4	B3	-N(CH ₃) ₂	-COOCH ₃	-S-	[2RS-(2α, 3αα, 11bβ)]

Table 2

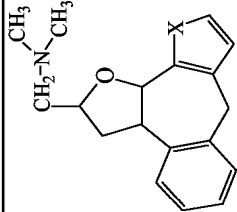
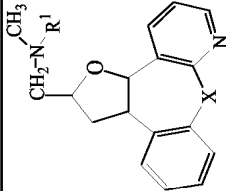
		
Co. No.	Ex. No.	Physical data
35	B1	mixture (80:15:5) of three diastereoisomers: (80) [2RS-(2α, 3α, 11bα)]; other diastereoisomers not assigned ; oxalate (1:1)

Table 3

				
Co. No.	Ex. No.	R ¹	X	Physical data
36	B1	-H	>N(benzyl)-	mixture (60:28:6:6) of four diastereoisomers: (60:28) [2RS-(3aβ, 11bα)], stereochemistry at position two not assigned ; (6:6) [2RS-3aα, 11bα)], stereochemistry at position two not assigned
37	B1	-H	>N(benzyl)-	mixture of two trans fused diastereoisomers, stereochemistry at position 2 not assigned

The LCMS data shown in Table 4 have been obtained by the following method:

The HPLC gradient was supplied by a HP 1100 from Agilent with a column heater set at 40 °C. Flow from the column was passed through photodiode array (PDA) detector and then split to a Light Scattering detector (ELSD) and to a Waters-Micromass Time of Flight (ToF) mass spectrometer with an electrospray ionization source operated simultaneously in positive and negative ionization mode.

Reversed phase HPLC was carried out on a XDB-C18 cartridge (3.5 µm, 4.6 x 30 mm) from Agilent, with a flow rate of 1 ml/min. Three mobile phases (mobile phase A: 0.5 g/l ammoniumacetate solution, mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 80 % A, 10 % B, 10 % C to 50 % B and 50 % C in 6.0 min., to 100 % B at 6.5 min., kept till 7.0 min and reequilibrated with 80 % A, 10 % B and 10 % C at 7.6 min. that was kept till 9.0 min. An injection volume of 5 µL was used.

High Resolution Mass spectra were acquired by scanning from 100 to 750 in 1 s using a dwell time of 1 s. The capillary needle voltage was 3 kV and the source temperature was maintained at 140 °C. Nitrogen was used as the nebulizer gas. Cone voltage was 30 V for both positive and negative ionization mode. Leucine-enkephaline was the reference used for the lock spray. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system. All parent peak masses correspond to the free base + H⁺.

Table 4

Co. No.	Retention time	Parent peak mass (ES+)	Mw calculated
14	4.17	318	317
15	4.53	403	402
16	4.20/4.25	360	359
17	5.7	416	415
18	4.48	348	347
19	4.32	318	317
20	3.52	304	303
2	4.46	318	317
21	3.74	304	303

-37-

Co. No.	Retention time	Parent peak mass (ES+)	Mw calculated
34	4.91	390	389
23	4.22/4.41	360	359
27	4.65	387	386
29	4.64	387	386
31	3.64	304	303
32	3.63	304	303
36	3.40/3.63/3.93/4.01	372	371
5	3.63	348	347

C. Pharmacological examples

Example C.1 : *In vitro* binding affinity for 5-HT_{2A} and 5-HT_{2C} receptors

- 5 The interaction of the compounds of Formula (I) with 5-HT_{2A} and 5-HT_{2C} receptors was assessed in *in vitro* radioligand binding experiments. In general, a low concentration of a radioligand with a high binding affinity for the receptor is incubated with a sample of a tissue preparation enriched in a particular receptor (1 to 5 mg tissue) in a buffered medium (0.2 to 5 ml). During the incubation, the radioligands bind to the receptor.
- 10 When equilibrium of binding is reached, the receptor bound radioactivity is separated from the non-bound radioactivity, and the receptor bound activity is counted. The interaction of the test compounds with the receptors is assessed in competition binding experiments. Various concentrations of the test compound are added to the incubation mixture containing the tissue preparation and the radioligand. Binding of
- 15 the radioligand will be inhibited by the test compound in proportion to its binding affinity and its concentration. The radioligand used for 5-HT_{2A} binding affinity is ³H-ketanserin and the tissue used is the frontal cortex of the rat. The radioligand used for 5-HT_{2C} binding affinity is ³H-mesulergine and the tissue used is the choroid plexus of the pig.

20

Example C.2 : *In vitro* determination of NET reuptake inhibition

- Cortex from rat brain was collected and homogenised using an Ultra-Turrax T25 and a Dual homogeniser in ice-cold homogenising buffer containing Tris, NaCl and KCl (50 mM, 120 mM and 5 mM, respectively, pH 7.4) prior to dilution to an appropriate protein concentration optimised for specific and non-specific binding. Binding was performed with radioligand [³H]Nixosetine (NEN, NET-1084, specific activity ~70
- 25

-38-

Ci/mmol) diluted in ice cold assay buffer containing Tris, NaCl and KCl (50 mM, 300 mM and 5 mM, respectively, pH 7.4). at a concentration of 20 nmol/L. Prepared radioligand (50 μ l) was then incubated (60 min, 25 °C) with membrane preparations pre-diluted to an appropriate protein concentration (400 μ l), and with 50 μ l of either the
5 10 % DMSO control, Mazindol (10^{-6} mol/L final concentration), or compound of interest. Membrane-bound activity was detected by filtration through a Packard Filtermate harvester onto GF/B Unifilterplates, washed with ice-cold Tris-HCl buffer, containing NaCl and KCl (50 mM, 120 mM and 4 mM; pH 7.4; 6 x 0.5 ml). Filters were allowed to dry for 24 h before adding scintillation fluid. Scintillation fluid was allowed to saturate
10 filters for 24 h before counting in a Topcount scintillation counter. Percentage specific bound and competition binding curves were calculated using S-Plus software (Insightful).

Example C.3 : *In vitro* binding affinity for human D_{2L} receptor

15 Frozen membranes of human Dopamine D_{2L} receptor-transfected CHO cells were thawed, briefly homogenised using an Ultra-Turrax T25 homogeniser and diluted in Tris-HCl assay buffer containing NaCl, CaCl₂, MgCl₂, KCl (50, 120, 2, 1, and 5 mM respectively, adjusted to pH 7.7 with HCl) to an appropriate protein concentration optimised for specific and non-specific binding. Radioligand [³H]Spiperone (NEN, specific activity ~70 Ci/mmol) was diluted in assay buffer at a concentration of 2 nmol/L. Prepared radioligand (50 μ l), along with 50 μ l of either the 10 % DMSO control, Butaclamol (10^{-6} mol/l final concentration), or compound of interest, was then incubated (30
20 min, 37 °C) with 400 μ l of the prepared membrane solution. Membrane-bound activity was filtered through a Packard Filtermate harvester onto GF/B Unifilterplates and washed with ice-cold Tris-HCl buffer (50 mM; pH 7.7; 6 x 0.5 ml). Filters were allowed to dry before adding scintillation fluid and counting in a Topcount scintillation counter. Percentage specific bound and competition binding curves were calculated using S-Plus software (Insightful).

30

Results

The results from the above assays are given in the following table as (pIC₅₀) values:
 “n.d.” means "not determined".

5 Table 5

Co.No.	5-HT _{2A}	5-HT _{2C}	D ₂	NET-inhibition
11	8.5	7.4	8.2	5.1
13	8.3	7.0	7.7	< 5
12	7.9	6.6	7.5	< 5
16	7.7	7.8	6.8	5.5
17	7.4	7.0	6.8	< 5
5	n.d.	7.7	6.7	6.4
25	8.0	8.0	6.7	6.9
10	7.9	7.7	6.7	6.7
2	> 8	8.1	6.7	7.2
15	6.7	6.6	6.6	5.6
23	> 8	8.4	6.6	5.5
27	n.d.	7.3	6.4	< 5
9	7.8	7.6	6.4	6.5
21	> 8	8.4	6.3	6.9
29	n.d.	6.6	6.1	< 5
35	8.2	7.8	6.1	6.3
33	7.0	7.3	6.1	6.0
18	7.4	7.4	6.0	7.5
20	7.1	7.3	5.9	7.2
19	7.0	7.6	5.9	7.5
31	n.d.	7.56	5.9	6.0
37	n.d.	7.0	5.8	5.9
32	n.d.	7.3	5.7	7.4
6	7.4	7.4	5.6	5.7
7	6.6	7.7	5.5	5.6
8	< 5	7.2	5.5	6.0
4	n.d.	6.8	5.4	6.2
34	6.8	6.5	5.4	5.6
36	n.d.	6.2	5.2	5.3
14	7.1	6.6	< 6	6.3

D. Composition examples

“Active ingredient” (A.I.) as used throughout these examples relates to a compound according to Formula (I), a pharmaceutically acceptable acid addition salt, a stereochemically isomeric form thereof or a *N*-oxide form thereof.

5

Example D.1 : ORAL SOLUTION

Methyl 4-hydroxybenzoate (9 g) and propyl 4-hydroxybenzoate (1 g) were dissolved in boiling purified water (4 l). In 3 l of this solution were dissolved first 2,3-dihydroxybutanedioic acid (10 g) and thereafter A.I (20 g). The latter solution was combined with the remaining part of the former solution and 1,2,3-propanetriol (12 l) and sorbitol 70% solution (3 l) were added thereto. Sodium saccharin (40 g) were dissolved in water (500 ml) and raspberry (2 ml) and gooseberry essence (2 ml) were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

15

Example D.2 : FILM-COATED TABLETS

Preparation of tablet core

A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinylpyrrolidone (10 g) in water (200 ml). The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

25

Coating

To a solution of methyl cellulose (10 g) in denaturated ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in dichloromethane (150 ml). Then there were added dichloromethane (75 ml) and 1,2,3-propanetriol (2.5 ml). Polyethylene glycol (10 g) was molten and dissolved in dichloromethane (75 ml). The latter solution was added to the former and then there were added magnesium octadecanoate (2.5 g), polyvinylpyrrolidone (5 g) and concentrated colour suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

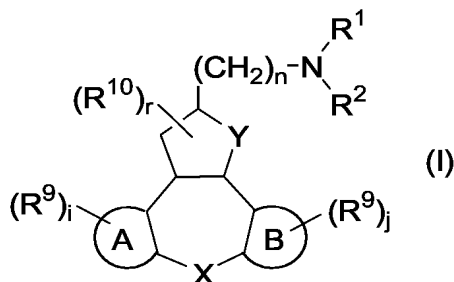
35

Example D.3 : INJECTABLE SOLUTION

Methyl 4-hydroxybenzoate (1.8 g) and propyl 4-hydroxybenzoate (0.2 g) were dissolved in boiling water (500 ml) for injection. After cooling to about 50°C there were added while stirring lactic acid (4 g), propylene glycol (0.05 g) and A.I. (4 g). The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1000 ml, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

Claims

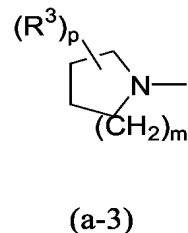
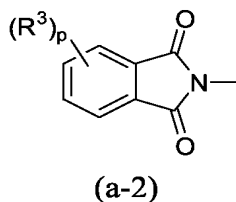
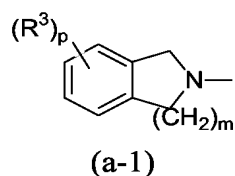
1. Compound according to Formula (I)



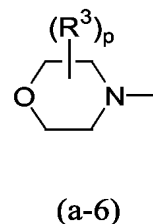
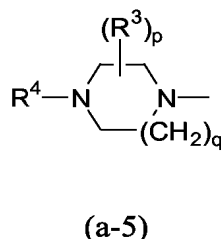
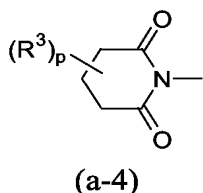
5

an *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

- n is an integer, equal to zero ; 1 ; 2 ; 3 ; 4 ; 5 or 6 ;
 10 i, j are integers, independently from each other, equal to zero ; 1 ; 2 ; 3 or 4 ;
 r is an integer, equal to zero ; 1 ; 2 ; 3 or 4 ;
 R^1 and R^2 each independently from each other, are hydrogen ; alkylcarbonyl ; alkyl ;
 ; alkyloxyalkyl ; alkylcarbonyloxyalkyl ; alkyloxycarbonylalkyl ; arylalkyl ;
 15 arylcarbonyl ; alkyloxycarbonyl ; aryloxycarbonyl ; arylalkylcarbonyl ; al-
 kyloxy-carbonylalkylcarbonyl ; mono- or di(alkyl)aminocarbonyl ; mono-
 or di(aryl)aminocarbonyl ; mono- or di(arylalkyl)aminocarbonyl ; mono- or
 di(alkyloxycarbonylalkyl)aminocarbonyl ; alkylsulphonyl ; arylsulphonyl ;
 arylalkylsulphonyl ; mono- or di(alkyl)aminothiocarbonyl ; mono- or
 di(aryl)aminothiocarbonyl ; mono- or di(arylalkyl)aminothiocarbonyl ;
 20 mono-, di- or tri(alkyl)amidino ; mono-, di- or tri(aryl)amidino and mono-,
 di- or tri(arylalkyl)amidino ; or R^1 and R^2 taken together with the nitrogen
 atom to which they are attached may form a radical of Formula:



-43-



wherein :

p is an integer equal to zero ; 1 ; 2 ; 3 or 4 ;

q is an integer equal to 1 or 2 ;

5 m is an integer equal to zero ; 1 ; 2 or 3 ;

each R³ independently from each other, is selected from the group of

halo ; hydroxy ; cyano ; alkyl ; alkyloxyalkyl ; aryloxyalkyl ; mono- or
 di(alkyl)aminoalkyl ; hydroxycarbonylalkyl ; alkyloxycarbonylalkyl ;
 mono- or di(alkyl)aminocarbonylalkyl ; mono- or di(aryl)-
 aminocarbonylalkyl ; mono- or di(alkyl)aminocarbonyloxyalkyl ; alky-
 loxycarbonyloxyalkyl ; arylaminocarbonyloxyalkyl ; arylalkylaminocar-
 bonyloxyalkyl ; aryl ; alkyloxy ; aryloxy ; alkylcarbonyloxy ; arylcar-
 bonyloxy ; arylalkylcarbonyloxy ; alkylcarbonyl ; arylcarbonyl ; ary-
 loxycarbonyl ; hydroxycarbonyl ; alkyloxycarbonyl ; mono- or di-
 alkylamino ; alkylcarbonylamino ; arylalkylcarbonylamino ; arylcarbonyl-
 amino ; alkyloxycarbonylamino ; aminocarbonylamino ; mono- or
 di(arylalkyl)aminocarbonylamino ; alkylsulphonylalkylamino-
 carbonylamino ; or

two R³-radicals may form together a bivalent radical

20 -CR⁵R⁵-CR⁵R⁵-O- (b-1)

-O-CR⁵R⁵-CR⁵R⁵- (b-2)

-O-CR⁵R⁵-CR⁵R⁵-O- (b-3)

-O-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵- (b-4)

-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-O- (b-5)

25 -O-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-O- (b-6)

-O-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵- (b-7)

-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-O- (b-8) and

-O-CR⁵R⁵-CR⁵R⁵-CR⁵R⁵-O- (b-9)

wherein R⁵ is selected from the group of hydrogen ; halo ; hydroxy ; al-
 30 kyloxy and alkyl ;

R⁴ is selected from the group of hydrogen ; alkyl ; arylalkyl ; alkyloxyalkyl
 ; alkylcarbonyloxyalkyl ; alkyloxycarbonylalkyl ; arylcarbonylalkyl ; al-

- kylsulphonyloxyalkyl ; aryloxyaryl ; alkyloxycarbonylaryl ; alkylcarbonyl ; arylalkylcarbonyl ; alkyloxycarbonylalkylcarbonyl ; arylcarbonyl ; alkyloxycarbonyl ; aryloxycarbonyl ; arylalkyloxycarbonyl ; mono- or di(alkyl)aminocarbonyl ; mono- or di(aryl)aminocarbonyl ;
 5 mono- or di(arylalkyl)aminocarbonyl ; mono- or di(alkyloxycarbonylalkyl)aminocarbonyl ; alkyloxyalkylaminocarbonyl ; mono-, di- or tri(alkyl)amidino ; mono-, di- or tri(aryl)amidino ; mono-, di- or tri(arylalkyl)amidino ; alkylsulphonyl ; arylalkylsulphonyl or arylsulphonyl ;
- 10 each R^{10} is independently from each other, alkyl or cyano ;
 A and B are, each independently from each other, aryl or an heteroaryl radical fused to the central ring and selected from the group of furyl ; thienyl ; pyrrolyl ; oxazolyl ; thiazolyl ; imidazolyl ; isoxazolyl ; isothiazolyl ; oxadiazolyl ; triazolyl ; pyridinyl ; pyridazinyl ; pyrimidinyl ; pyrazinyl ;
 15 indolyl ; indolizinyll ; isoindolyl ; benzofuryl ; isobenzofuryl ; benzothienyl ; indazolyl ; benzimidazolyl ; benzthiazolyl ; quinolizinyll ; quinolinyl ; isoquinolinyl ; phthalazinyl ; quinazolinyl ; quinoxalinyll ; chromenyl ; naphthyridinyl and naphthalenyl ; providing at least one of A and B is one of the above heteroaryl radicals ;
- 20 each R^9 is, independently from each other, selected from the group of hydrogen ; halo ; cyano ; hydroxy ; carboxyl ; nitro ; amino ; mono- or di(alkyl)amino ; alkylcarbonylamino ; aminosulfonyl ; mono- or di(alkyl)aminosulfonyl ; alkyl ; alkenyl ; alkyloxy ; alkylcarbonyl and alkyloxycarbonyl ;
- 25 Y represents O ; S ; S(=O) ; S(=O)₂ or NR⁸ ;
 X represents CR⁶R⁷ ; O ; S ; S(=O) ; S(=O)₂ or NR⁸ ; wherein
 R⁶ and R⁷ each independently are selected from the group of hydrogen ; hydroxy ; alkyl and alkyloxy ; or
 R⁶ and R⁷ taken together may form a radical selected from the group of methylene(i.e. =CH₂) ; mono- or di(cyano)methylene ; a bivalent radical of
 30 Formula-(CH₂)₂- ; -(CH₂)₃- ; -(CH₂)₄- ; -(CH₂)₅- ; -O-(CH₂)₂-O- ; -O(CH₂)₃O- ; or, together with the carbon atom to which they are attached, a carbonyl ;
- 35 R⁸ is selected from the group of hydrogen ; alkyl ; alkylcarbonyl ; arylcarbonyl ; arylalkyl ; arylalkylcarbonyl ; alkylsulfonyl ; arylsulfonyl and arylalkylsulfonyl ;

- aryl is phenyl or naphthyl, each optionally substituted with 1, 2 or 3 substituents selected from the group of halo ; nitro ; cyano ; hydroxy ; alkyloxy or alkyl ;
 alkyl represents a straight or branched saturated hydrocarbon radical having from 1 to 10 carbon atoms, a cyclic saturated hydrocarbon radical having from 3 to 8 carbon atoms or a saturated hydrocarbon radical containing a straight or branched moiety having from 1 to 10 carbon atoms and a cyclic moiety having from 3 to 8 carbon atoms ; each radical optionally substituted with one or more halo ; cyano ; oxo ; hydroxy ; formyl ; carboxyl or amino radicals ;
 alkenyl represents a straight or branched unsaturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic unsaturated hydrocarbon radical having from 3 to 6 carbon atoms ; said radical having one or more double bonds and said radical being optionally substituted with one or more halo ; cyano ; oxo ; hydroxy ; formyl ; carboxyl or amino radicals ; and
 halo represents fluoro ; chloro ; bromo and iodo.
2. Compound according to Claim 1, characterized in that R^1 and R^2 each, independently from each other, are hydrogen or alkyl, each alkyl radical optionally substituted with hydroxy ; or R^1 and R^2 taken together with the nitrogen atom to which they are attached, to form a radical of Formula (a-3) or (a-5), wherein m = an integer, equal to 1 or 2.
 3. Compound according to any one of Claims 1 to 2, characterized in that A and B, each independently from each other, is aryl or an heteroaryl radical selected from thienyl and pyridinyl, providing that at least one of A and B is an heteroaryl radical.
 4. Compound according to Claim 3, characterized in that A is aryl and B is thienyl wherein S is at position 9 or 11.
 5. Compound according to Claim 4, characterized in that X is S.
 6. Compound according to any one of Claims 1 to 5, characterized in that Y is O.
 7. Compound according to any one of Claims 1 to 6, characterized in that Y is CR^6R^7 , O, S, $S(=O)$, $S(=O)_2$ or NR^8 .

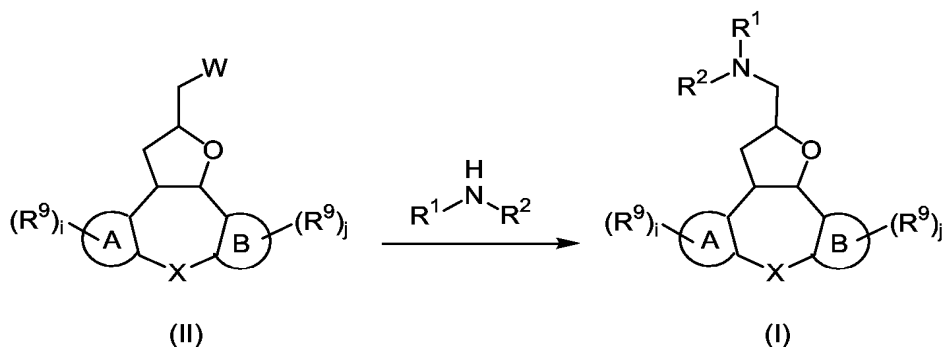
8. Compound according to any one of Claims 1 to 7, characterized in that
- n is an integer equal to 1 ;
- i is an integer equal to 0 ;
- 5 j is an integer equal to 0 or 1 ;
- r is an integer equal to 0 ;
- R¹ and R² are, each independently from each other, hydrogen, methyl, ethyl, or hydroxyethyl ;
- A is phenyl ;
- 10 B is thienyl or pyridinyl
- R⁹ is hydrogen ;
- R¹⁰ is hydrogen, hydroxymethyl, methoxycarbonyl or ethoxycarbonyl ;
- Y is O ;
- X is CH₂, S or *N*-benzyl.
- 15
9. Compound according to any one of claims 1 to 8 for use as a medicine.
10. Pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a therapeutically effective amount of a compound according to any one of claims 1 to 9.
- 20
11. Use of a compound according to any one of claims 1 to 9 for the manufacture of a medicament for the prevention and/or treatment of conditions mediated through the 5HT₂ receptor, in particular 5HT_{2A} and 5HT_{2C} receptor and D₂ receptor, as well as the through norepinephrine reuptake inhibition.
- 25
12. Use of a compound according to any one of claims 1 to 9 for the manufacture of a medicament for the treatment and/or prevention of central nervous system disorders like anxiety ; depression and mild depression ; bipolar disorders ; sleep- and sexual disorders ; psychosis ; borderline psychosi ; schizophrenia ; migraine ; personality disorders ; obsessive-compulsive disorders ; social phobias ; panic attacks; attention disorders ; organic mental disorders ; mental disorders in children ; aggression ; memory disorders and attitude disorders, especially in older people ; addiction ; obesity bulimia and similar disorders.
- 30
- 35

13. Use of a compound according to any one of claims 1 to 9 for the manufacture of a medicament for the treatment and/or prevention of anxiety, psychosis, depression, bipolar disorders including bipolar depression, migraine and addictive properties of drugs of abuse.

5

14. Process for the preparation of a compound according to Formula (I), characterized by *N*-alkylating an intermediate of Formula (II), wherein R^9 , i , j , ring A, ring B and X all have the meaning as defined in Formula (I) and wherein W represents a suitable leaving group, with an amine of Formula HNR^1R^2 , wherein R^1 and R^2 are defined as in Formula (I), in a reaction-inert solvent and optionally in the presence of a suitable base ;

10



- 15 and, if desired, converting compounds of Formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of Formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, *N*-oxides thereof and quaternary ammonium salts thereof.
- 20

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/050444

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D495/14 C07D495/04 C07D491/14 A61K31/55 A61K31/381
A61K31/38 A61P25/18 A61P25/22 A61P25/24 A61P25/30
A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/38991 A (JANSSEN PHARMACEUTICA N.V.; GIL-LOPETEGUI, PILAR; FERNANDEZ-GADEA, FRAN) 23 October 1997 (1997-10-23) cited in the application Claims 1-13; Formula (I); p. 9, l. 5-28; compounds 1-9	1-14
Y	WO 97/39001 A (JANSSEN PHARMACEUTICA N.V.; ANDRES-GIL, JOSE IGNACIO; MARTINEZ, PEDRO;) 23 October 1997 (1997-10-23) cited in the application Claims 1-8; Formula (I); p. 9, l. 13-35; compounds 1-10	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

8 May 2006

Date of mailing of the international search report

16/05/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kirsch, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/050444

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9738991	A	23-10-1997	AT 236893 T	15-04-2003
			AU 712154 B2	28-10-1999
			AU 2695997 A	07-11-1997
			BG 63083 B1	30-03-2001
			BG 102820 A	31-08-1999
			BR 9706639 A	12-01-1999
			CA 2232141 A1	23-10-1997
			CN 1205006 A	13-01-1999
			CY 2382 A	04-06-2004
			CZ 9803243 A3	13-01-1999
			DE 69720709 D1	15-05-2003
			DE 69720709 T2	11-03-2004
			DK 892793 T3	21-07-2003
			EA 1002 B1	28-08-2000
			EE 9800326 A	15-04-1999
			ES 2196328 T3	16-12-2003
			HK 1015771 A1	25-07-2003
			HU 9901613 A2	28-09-1999
			IL 123655 A	19-03-2001
			JP 3199751 B2	20-08-2001
			JP 2000508327 T	04-07-2000
			NO 981076 A	09-10-1998
			NZ 329953 A	29-06-1999
			PL 328575 A1	01-02-1999
			PT 892793 T	29-08-2003
			SK 141898 A3	10-03-1999
			TR 9801164 T2	21-10-1998
			TW 504506 B	01-10-2002
			US 6057441 A	02-05-2000
			US 6194405 B1	27-02-2001
			ZA 9703114 A	12-10-1998
WO 9739001	A	23-10-1997	AT 222911 T	15-09-2002
			AU 716470 B2	24-02-2000
			AU 2385297 A	07-11-1997
			CA 2232195 A1	23-10-1997
			CN 1205010 A	13-01-1999
			DE 69714980 D1	02-10-2002
			DE 69714980 T2	10-04-2003
			DK 892804 T3	02-12-2002
			ES 2182064 T3	01-03-2003
			HU 9901875 A2	28-09-1999
			IL 123656 A	13-09-2001
			JP 2000508328 T	04-07-2000
			NO 981077 A	12-10-1998
			NZ 329954 A	29-07-1999
			PL 326871 A1	26-10-1998
			PT 892804 T	31-01-2003
			TW 514637 B	21-12-2002
			US 6156747 A	05-12-2000
			ZA 9703122 A	12-10-1998

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
3 August 2006 (03.08.2006)

PCT

(10) International Publication Number
WO 2006/079637 A1

(51) International Patent Classification:

C07D 495/14 (2006.01) A61P 25/18 (2006.01)
C07D 495/04 (2006.01) A61P 25/22 (2006.01)
C07D 491/14 (2006.01) A61P 25/24 (2006.01)
A61K 31/55 (2006.01) A61P 25/30 (2006.01)
A61K 31/381 (2006.01) A61P 3/04 (2006.01)
A61K 31/38 (2006.01)

(74) Common Representative: JANSSEN PHARMACEUTICA N.V.; Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:

PCT/EP2006/050444

(22) International Filing Date: 25 January 2006 (25.01.2006)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

05100547.8 27 January 2005 (27.01.2005) EP

(71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CID-NÚÑEZ, José, Maria [ES/ES]; c/o Johnson & Johnson Pharmaceutical Research and Development, Poligono Industrial, Calle Jarama, 75, 45007 Toledo (ES). MEGENS, Antonius, Adrianus, Hendrikus, Petrus [NL/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). TRABANCO-SUÁREZ, Andrés, Avelino [ES/ES]; c/o Johnson & Johnson Pharmaceutical Research and Development, Poligono Industrial, Calle Jarama, 75, 45007 Toledo (ES).

Published:

— with international search report

(48) Date of publication of this corrected version:

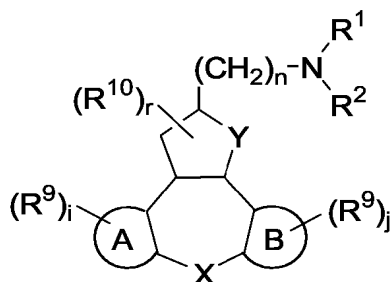
16 August 2007

(15) Information about Correction:

see PCT Gazette No. 33/2007 of 16 August 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROCYCLIC TETRACYCLIC TETRAHYDROFURAN DERIVATIVES AS 5HT2 INHIBITORS IN THE TREATMENT OF CNS DISORDERS



(I)

(57) Abstract: This invention concerns novel substituted heterocyclic tetracyclic tetrahydrofuran derivatives with binding affinities towards serotonin receptors, in particular 5-HT2A and 5-HT2C receptors, and towards dopamine receptors, in particular dopamine D2 receptors and with norepinephrine reuptake inhibition properties, pharmaceutical compositions comprising the compounds according to the invention, the use thereof as a medicine, in particular for the prevention and/or treatment of a range of psychiatric and neurological disorders, in particular certain psychotic, cardiovascular and gastrokinetic disorders and processes for their production. The compounds according to the invention can be represented by general Formula (I), and comprises also the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form

thereof and prodrugs thereof, wherein all substituents are defined as in Claim 1.

WO 2006/079637 A1